25538

Cancer Causes and Control, 1997, 8, pp. 229-238

Association of smoking, body mass, and physical activity with risk of prostate cancer in the Iowa 65+ Rural Health Study (United States)

James R. Cerhan, James C. Torner, Charles F. Lynch, Linda M. Rubenstein, Jon H. Lemke, Michael B. Cohen, David M. Lubaroff, and Robert B. Wallace

(Received 23 August 1996; accepted in revised form 18 December 1996)

Smoking, obesity, alcohol, and physical activity can modulate the endocrine system, and therefore have been hypothesized to play a role in the etiology of prostate cancer. At baseline in 1982, 80 percent ($n = 3,673$) of the noninstitutionalized persons age 65+ in two rural Iowa (United States) counties were enrolled into the Iowa 65+ Rural Health Study. Follow-up for mortality was complete through 1993, and cancer experience was determined by linkage to the State Health Registry of Iowa cancer database for the years 1973-93. We analyzed data on 1,050 men aged 65 to 101 years (mean age 73.5) with a full interview in 1982 and with no documented cancer in the 10 years prior to baseline. Through 1993 (8,474 person-years of follow-up), there were 71 incident cases of prostate cancer. In a multivariate model, age, cigarette smoking (relative risk [RR] = 2.9 for currently smoking 20 or more cigarettes per day compared with never smoking; P trend = 0.009), greater body mass index (BMI) (wt/ht^2) (RR = 1.7 for BMI > 27.8 kg/m^2 compared with < 23.6; P trend = 0.1), and greater level of physical activity (RR = 1.9 for high activity level *cf* inactive; P trend = 0.05) were independent predictors of prostate cancer, and these associations were stronger for regional or disseminated disease at diagnosis. Percent change in BMI from age 50 to baseline was associated positively with risk (P trend = 0.01), and this association appeared to be stronger in heavier men. There were no data on diet. These findings suggest that smoking, overweight, and weight gain in later life are risk factors for prostate cancer and support a hormonal etiology; the positive association for physical activity confirms some previous reports, but remains without a credible biologic mechanism. *Cancer Causes and Control* 1997, 8, 229-238

Key words: Men, smoking, physical activity, prostate neoplasms, United States, weight.

Authors are with the University of Iowa College of Medicine, Iowa City, IA, USA. Drs Cerhan, Torner, Lynch, Rubenstein, Lemke, and Wallace are with the Department of Preventive Medicine and Environmental Health; Dr Cohen is with the Department of Pathology; Drs Cohen and Lubaroff are with the Department of Urology; Dr Wallace is with the Cancer Center. Address correspondence to Dr Cerhan, Department of Preventive Medicine and Environmental Health, 2800 Steindler Building, The University of Iowa College of Medicine, Iowa City, IA, 52242-1008, USA. *This work was supported by grant R21 CA/ES69838 from the US National Cancer Institute. The Iowa 65+ Rural Health Study was supported by grants AG-O-2106, AG10127 and AG09682 from the US National Institute on Aging. Dr Cerhan was supported in part by a US National Cancer Institute Preventive Oncology Academic Award (K07 CA64220). Portions of this work were presented at the North American Association of Central Cancer Registries 1996 Annual Conference, Minneapolis, MN (USA), April 17-19, 1996.*

Introduction

Prostate cancer is the most commonly diagnosed non-cutaneous cancer in men in the United States and it is especially common in elderly men, where the peak incidence rate of 1,490 per 100,000 occurs in the 80-84 year age group.[1] Current theories of the etiology of this disease derive from several striking epidemiologic observations. There is approximately a 50-fold difference between populations with high incidence (*e.g.*, US and Sweden) and low incidence (*e.g.*, China, Singapore) of prostate cancer.[2] However, autopsy studies reveal that the prevalence of histologic prostate cancer in men over age 50 is between 15 and 30 percent, and this prevalence rate appears to be consistent across populations.[3-4]

These observations suggest that initiating events for prostate carcinogenesis may be relatively common across different populations, but that there are likely to be large differences in exposure to factors which promote growth, invasion, or metastasis leading to clinically evident prostate cancer. This hypothesis is consistent with migration studies which document an increase in prostate cancer risk in persons who move from areas with a low incidence to areas with higher incidence.[3-4] In addition, prostate cancer has not been reported in eunuchs,[5-6] and hormonal manipulation has been used widely in the palliative treatment of prostate cancer.[7] These and other[8] observations suggest that endogenous hormones are likely to play a fundamental role in carcinogenesis in the prostate gland. We therefore prospectively evaluated the role of constitutional (*i.e.*, height, weight, and body mass) and lifestyle (*i.e.*, smoking, alcohol, and physical activity) factors known to modulate the endocrine system as prostate cancer risk factors in a cohort of rural elderly men.

Materials and methods

Study population

In late 1981 and 1982, 80 percent of the noninstitutionalized residents aged 65 years and older who lived in Iowa and Washington counties, Iowa (US), were enrolled into the Iowa 65+ Rural Health Study ($n = 3{,}673$), which was one of the four Established Populations for Epidemiologic Studies of the Elderly (EPESE) sites.[9,10] These two counties are primarily rural, with several small towns. Of the 1,420 men enrolled into the cohort, only the 1,155 men completing the full-form baseline interview were eligible for inclusion into this report. The full-form baseline interview was conducted in the respondent's home by a trained interviewer, and included data on a variety of demographic, health, and social characteristics.

Data collection

Demographic and lifestyle characteristics ascertained included age, number of years of education, marital status, detailed smoking history, and current alcohol use (beer, wine, and liquor). Height at baseline and weight at baseline, age 50, and age 25 were self-reported, and baseline body mass index (BMI) was calculated as baseline weight divided by baseline height^2; BMI at age 25 and 50 were calculated using weights at their respective ages and height reported at baseline.

Level of physical activity was classified as inactive, moderately active, and highly active, and was based on a scale from a previously published EPESE report.[11] The scale included the following five items: 'How often do you: garden or do yardwork in season?; do housework?; take walks?; jog, bike ride, swim or do other vigorous exercise?; play horse shoes/golf or play other moderate exercise games in season?' Possible responses to each question were 'do not do,' 'everyday,' 'several times a week,' 'once a week,' 'several times a month,' or 'once a month or less.' Men who reported engaging in vigorous or moderate exercise at least weekly were classified as highly active; men who walked at least several times per week *or* walked weekly and gardened at least several times per week and did housework at least several times per week *or* who walked weekly and did vigorous or moderate activity several times per month were classified as moderately active; and men who met none of the above criteria were classified as inactive. We did not have information on activities not related to recreation or home maintenance, although only seven percent of men were employed full-time at baseline examination. The most common activity was walking, and the range of this activity was thought to be very broad. Therefore, the active group was divided into high *of* moderate activity based on participation in vigorous sport or exercise to better discriminate average activity levels.[11]

Physical function was assessed by self-report of ability to do heavy work around the house, walk up and down a flight of stairs, or walk a half mile without help, and was based on the Rosow-Breslau Functional Health Scale.[12] In a further analysis of physical activity, men with one or more physical disabilities were coded into a separate category, so that the evaluation of physical activity focused on men who were physically capable of engaging in physical activity.

Cohort follow-up

Cohort members were contacted annually by either telephone interviews (follow-ups at years 1, 2, 4, 5, and 7) or by in-person interviews (follow-ups at years 3, 6, and 10) to update risk factor information and to update residence and vital status. Vital status also was followed passively through monitoring of local obituary notices and state vital records and was known for all participants through 31 December 1993.

The cancer experience of the cohort, except for non-melanoma skin cancer, was ascertained by linking the entire cohort to the State Health Registry of Iowa's cancer database, which is part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program.[1] The registry collects data, including identifying information, tumor site, morphology, and extent of disease, on all persons who are Iowa residents at the time of their diagnosis. Topographic and morphologic data were coded using the International Classification of Diseases for Oncology (ICD-O), Second Edition.[13] Linkage was conducted for the years 1973 through 1993, and was based on a combination of social security number, first and last names, date of birth, city, and zip code.

Statistical analysis

Of the 1,155 men who completed a full-form baseline interview, we excluded men with any cancer in the registry between 1973 and the baseline interview ($n = 101$), or who additionally self-reported a prostate cancer at any time prior to baseline ($n = 4$) before data analysis. This approach is likely to have excluded the vast majority of prevalent cancers (diagnosed after 1972) at study inception, as 90 percent of the men had lived in their baseline community 10 years or longer. This approach also decreased the reliance on lifetime self-report of cancer, which is known to be of questionable validity in this cohort.

Because we could only ascertain cancers occurring in Iowa residents, each man was allocated person-years of follow-up from the date of his baseline survey to the date of prostate cancer diagnosis (ICD-O code C61.9), date of emigration from Iowa, or date of death. If none of these occurred, follow-up was through 31 December 1993. Of the at-risk cohort of 1,050 men, 1.4 percent were censored because of a move from Iowa and 53 percent were censored because of death. The major underlying causes of death as reported on the death certificate included coronary heart disease (34 percent), cancer (19 percent), other cardiovascular disease (16 percent), respiratory disease (nine percent), and stroke (six percent).

Variables of interest were either categorized into natural categories or categories based on quartile cut-points of the distribution for the entire at-risk cohort. Incidence rates were calculated by dividing the number of events by the numbers of person-years of follow-up for the categories of interest. Relative risks (RR) and 95 percent confidence intervals (CI) were used as the measure of association; the Mantel-Haenszel procedure[14] was used for age-adjusted results and Poisson regression[15] was used for multivariable models. Analyses were conducted using SAS (SAS Institute, Cary, North Carolina, USA) and EGRET (SERC, Seattle, WA, USA).

Results

There were 1,050 men with a mean age of 73.5 years (range 65-101) who had no cancer in the cancer registry between 1973 and their baseline interview, and who had no self-report of a prior prostate cancer. Through 1993 (8,474 person-years) there were 71 cases of histologically confirmed prostate cancer. The mean age at diagnosis was 79.2 years (median, 78.8; range, 66-93). Based on the SEER staging codes,[1] 61 percent of the cases were staged as local, 24 percent were regional or distant, and 15 percent were unstaged. Cases, compared with non-cases, were more

Table 1. Descriptive characteristics of prostate cancer cases and non-cases at baseline interview, Iowa 65+ Rural Health Study, 1982-93[a]

Characteristic	Cases ($n = 71$)	Non-cases ($n = 979$)
Mean age (years)	73.5	73.5
Education		
Less than high school	42%	46%
High school	41%	38%
Greater than high school	14%	16%
Marital status		
Currently married	78%	82%
Formerly married	18%	14%
Never married	4%	4%
Mean weight (kg)	81.3	78.8
Mean height (m)	1.74	1.76
Mean BMI (kg/m^2) at baseline	26.5	25.6
Cigarette smoking status		
Never	37%	42%
Former	42%	44%
Current	21%	14%
Pack-years of smoking	30.8	26.3
Cigar smoking		
Never	68%	62%
Ever	31%	37%
Pipe smoking		
Never	65%	62%
Ever	34%	37%
Level of physical activity		
Inactive	27%	36%
Moderately active	41%	39%
Very active	32%	24%
Physical disabilities		
None	69%	66%
Any	31%	32%
Level of physical activity in the physically capable		
Inactive	17%	21%
Moderately active	28%	27%
Very active	24%	18%
Any physical disability	31%	32%

[a] Percent totals may not sum to 100 due to missing values or rounding.

2063634040

Table 2. Age-adjusted relative risks of prostate cancer according to anthropometric factors, The Iowa 65+ Rural Health Study, 1982-93

	Cases[a]	Person years	RR[b]	95% CI
Height (meters)				
< 1.73	23	2,280	1	—
1.73-1.77	19	2,446	0.8	(0.4-1.4)
1.78-1.80	14	2,301	0.6	(0.3-1.2)
> 1.80	15	1,420	1.1	(0.6-2.0)
			$P = 0.8$	
Weight (kg)				
< 70.8	15	2,020	1	—
70.8-77.9	17	2,018	1.2	(0.6-2.4)
78.0-86.3	17	2,554	1.0	(0.5-2.0)
> 86.3	21	1,833	1.6	(0.8-3.2)
			$P = 0.2$	
BMI (kg/m^2)				
< 23.6	16	2,005	1	—
23.6-25.8	15	2,223	0.9	(0.4-1.8)
25.9-27.8	17	2,118	1.1	(0.6-2.3)
> 27.8	22	2,065	1.5	(0.8-3.0)
			$P = 0.1$	
BMI (kg/m^2) at age 25				
< 20.9	14	1,881	1	—
20.9-22.4	15	2,144	1.0	(0.5-2.0)
22.5-24.4	15	1,873	1.1	(0.5-2.3)
> 24.4	21	2,029	1.4	(0.7-2.8)
			$P = 0.3$	
BMI (kg/m^2) at age 50				
< 22.9	15	1,947	1	—
22.9-24.4	18	2,181	1.1	(0.6-2.2)
24.5-27.1	16	2,034	1.0	(0.5-2.1)
> 27.1	20	2,046	1.3	(0.7-2.6)
			$P = 0.4$	
Percent change in BMI from age 25 to baseline				
< 5% change or loss	24	2,255	1	—
5-20% gain	23	3,054	0.7	(0.4-1.3)
> 20% gain	18	2,614	0.7	(0.4-1.4)
			$P = 0.3$	
Percent change in BMI from age 50 to baseline				
> 10% loss	3	756	0.4	(0.1-1.4)
5-10% loss	5	838	0.7	(0.3-1.7)
Within 5%	29	3,471	1	—
5-10% gain	12	1,257	1.2	(0.6-2.3)
> 10% gain	20	1,881	1.3	(0.7-2.2)
			$P = 0.04$	

[a] May not sum to 71 cases due to missing data.

[b] Adjusted for age (< 70, 70-74, 75-79, 80-84, 85+) by the method of Mantel and Haenszel. All P-values are for the trend test.

likely to be heavier, current smokers, and physically active, but were similar in terms of baseline age, level of education, height, blood pressure, and level of physical disability (Table 1).

Age-adjusted analyses

Weight and BMI both showed a suggestive positive association with prostate cancer risk, although the RR estimates were elevated only for the heaviest men and the point estimates were not statistically significant (Table 2). The associations for BMI at age 25 or age 50 were even

Table 3. Age-adjusted relative risks of prostate cancer according to smoking and alcohol history, The Iowa 65+ Rural Health Study, 1982-93

	Cases[a]	Person years	RR[b]	95% CI
Smoking status				
Never smoked	26	3,705	1	—
Former smoker	30	3,698	1.2	(0.7-2.1)
Current smoker	15	1,046	2.2	(1.2-4.4)
			$P = 0.02$	
Pack-years of smoking				
Never	26	3,705	1	—
< 31 pack-years	14	1,607	1.3	(0.7-2.5)
31-55 pack-years	12	1,445	1.3	(0.7-2.7)
> 55 pack-years	16	1,254	2.0	(1.1-3.8)
			$P = 0.04$	
No. of cigarettes currently smoked per day				
Never smoked	26	3,705	1	—
Former smoker	30	3,698	1.2	(0.7-2.1)
Current, < 20/day	6	521	1.8	(0.7-4.4)
Current, ≥ 20/day	9	525	2.7	(1.2-6.0)
			$P = 0.007$	
Years since quitting smoking				
Never smoked	26	3,705	1	—
Quit, ≥ 15 years ago	17	1,884	1.3	(0.7-2.5)
Quit, < 15 years ago	13	1,813	1.1	(0.6-2.2)
Current smoker	15	1,046	2.2	(1.2-4.4)
			$P = 0.03$	
Smoked cigars				
Never	48	6,484	1	—
Ever	22	1,937	1.5	(0.9-2.6)
Smoked a pipe				
Never	46	5,503	1	—
Ever	24	2,910	1.0	(0.6-1.6)
Alcohol consumption				
Never	22	2,235	1	—
Former	6	1,047	0.6	(0.3-1.6)
Current	39	4,060	1.0	(0.6-1.8)

[a] May not sum to 71 cases due to missing data.

[b] Adjusted for age (< 70, 70-74, 75-79, 80-84, 85+) by the method of Mantel and Haenszel. All P-values are for the trend test.

2063634041

weaker than the association for BMI at baseline, and there was no association with height. There was no association with percent change in BMI from age 25 to baseline interview, but there was a positive association between percent change in BMI from age 50 to baseline (P trend = 0.04). Compared with men whose BMI changed less than five percent between age 50 and baseline, men with a greater than 10 percent loss had an RR of 0.4 (CI = 0.1-1.4) while men with a greater than 10 percent gain had an RR of 1.3 (CI = 0.7-2.2).

Men who were current smokers at baseline had over a doubling of risk compared with nonsmokers, while former smokers had only a 20 percent elevation in risk which was not statistically significant (Table 3). There was a dose-response with pack-years of smoking (P trend = 0.04) and number of cigarettes currently smoked (P trend = 0.007), but most of the excess risk appeared to be associated with current smoking, as risk for former smokers remained only slightly elevated and was not associated consistently with time since quitting smoking. Smoking a cigar (RR = 1.5), but not a pipe (RR = 1.0) was associated with a statistically nonsignificant elevated risk. There was no association with current consumption of alcohol (Table 3) or individually with beer, wine, or liquor (data not shown).

Level of physical activity was associated positively with risk of prostate cancer (Table 4); compared with men who were inactive, men who were moderately active (RR = 1.4) or highly active (RR = 1.6) had elevated risk, although the point estimates and the trend test were not statistically significant. There was no association with the presence of any physical disability. When we evaluated physical activity in the physically capable, we found essentially the same associations for level of physical activity, and an increase in risk for men with any physical disability compared with physically capable inactive men (RR = 1.6).

Table 4. Age-adjusted relative risks of prostate cancer according to physical activity and physical function, The Iowa 65+ Rural Health Study, 1982-93

	Cases[a]	Person years	RR[b]	95% CI
Level of physical activity				
Inactive	19	2,856	1	—
Moderately active	29	3,223	1.4	(0.8-2.6)
Very active	23	2,329	1.6	(0.9-3.0)
			$P = 0.1$	
Presence of physical disabilities				
None	49	6,235	1	—
Any	22	2,174	1.2	(0.7-2.0)
Level of physical activity in the physically capable				
Inactive	12	1,991	1	—
Moderately active	20	2,431	1.4	(0.7-3.0)
Very active	17	1,877	1.5	(0.7-3.3)
			$P = 0.2$	
Any physical disability	22	2,174	1.6	(0.8-3.2)

[a] May not sum to 71 cases due to missing data.
[b] Adjusted for age (< 70, 70-74, 75-79, 80-84, 85+) by the method of Mantel and Haenszel. All P-values are for the trend test.

Multivariate analyses

The final multivariate model containing age, BMI, smoking, and physical activity is presented in Table 5. Increasing age ($P = 0.01$), BMI (P trend = 0.1), number of cigarettes currently smoked (P trend = 0.009), and physical activity (P trend = 0.05) all showed positive associations with risk, and the multivariate RRs were similar to or slightly stronger than the age-adjusted RRs. There were no statistically significant ($P < 0.05$) first-order interactions among these variables. In separate multivariate analyses stratified by level of physical activity, the associations for BMI were similar in inactive men (RR = 1.9 for the highest quartile of BMI compared with the lowest; P trend = 0.2) and active men (RR = 1.6 for the highest quartile of BMI compared with the lowest; P trend = 0.2). There were no important differences in the multivariate RRs presented for all prostate cancer in Table 5 after excluding men with full-time ($n = 71$) or part-time ($n = 169$) employment at baseline.

We next stratified the outcome by local disease at diagnosis ($n = 42$) *cf* regional or disseminated disease at diagnosis ($n = 17$) in order to address the potential for a detection bias. Such a bias would exist if more highly active men also were more likely to engage in routine screening for prostate cancer (and hence be diagnosed with an earlier stage cancer) or if current smokers were more likely to be diagnosed with an earlier stage cancer due to more frequent contact with the health care system. As seen in Table 5, even with sparse data the associations were stronger for regional or disseminated disease at diagnosis compared with localized disease at diagnosis, arguing against a strong role for a detection bias in these data.

We next evaluated whether smoking, BMI, and physical activity were risk factors for more aggressive tumors. Aggressive tumors are much more likely to be fatal, and therefore are of greater public health importance. Also, as discussed previously, it has been suggested that aggressive tumors are more likely to be associated with environmental factors. Following West and colleagues,[16] we defined aggressive tumors as any tumor with: (i) regional or distant stage at diagnosis; (ii) unknown stage with poorly or undifferentiated grade; or (iii) local stage with undifferentiated grade. There were only three additional cases beyond the 17 with regional or disseminated stage in Table 5 who met the criteria, and point-estimates

2063634042

Table 5. Multivariate-adjusted relative risks of prostate cancer, The Iowa 65+ Rural Health Study, 1982-93

Variable	All prostate cancer (n = 69)			Localized disease (n = 42)			Regional/distant disease (n = 17)		
	Cases	RR[a]	(CI)	Cases	RR[a]	(CI)	Cases	RR[a]	(CI)
Age (per 5 yrs)	69	1.3	(1.1-1.6)	42	1.2	(0.9-1.5)	17	1.8	(1.2-2.6)
BMI (kg/m^2)									
< 23.6	16	1	—	9	1	—	3	1	—
23.6-25.8	15	0.9	(0.5-1.9)	9	1.0	(0.4-2.5)	4	1.6	(0.3-7.4)
25.9-27.8	17	1.2	(0.6-2.5)	10	1.2	(0.5-3.1)	5	2.8	(0.6-13)
> 27.8	21	1.7	(0.8-3.3)	14	1.9	(0.8-4.5)	5	3.1	(0.7-14)
		P = 0.1			P = 0.1			P = 0.1	
Smoking status									
Never smoked	25	1	—	17	1	—	5	1	—
Former smoker	30	1.3	(0.8-2.2)	16	1.0	(0.5-2.0)	7	1.8	(0.6-5.8)
Current, < 20 cigs/day	6	2.0	(0.8-5.0)	4	1.9	(0.6-5.7)	2	4.7	(0.8-26)
Current, 20+ cigs/day	8	2.9	(1.3-6.7)	5	2.5	(0.9-7.1)	3	8.7	(1.9-40)
		P = 0.009			P = 0.09			P = 0.004	
Physical activity									
Inactive	18	1	—	11	1	—	4	1	—
Moderate activity	28	1.5	(0.8-2.8)	17	1.5	(0.7-3.2)	7	1.9	(0.5-6.5)
High activity	23	1.9	(1.0-3.5)	14	1.8	(0.8-4.1)	6	2.7	(0.7-9.9)
		P = 0.05			P = 0.1			P = 0.1	

[a] Multivariate relative risk (RR) from Poisson regression; CI = 95% confidence intervals. All P-values are for the trend test.

Table 6. Multivariate-adjusted relative risk of prostate cancer by BMI at age 50 and percent change in BMI from age 50 to Baseline, The Iowa 65+ Rural Health Study, 1982-93

BMI (kg/m^2) at age 50	Percent change in BMI from age 50 to baseline					BMI at age 50
	> 10% loss	5-10% loss	Within 5%	5-10% gain	> 10% gain	
≤ 24.4						
Relative risk[a]	0.5	0.5	1	1.7	1.2	1
95% confidence interval	(0.06-3.6)	(0.06-3.5)	—	(0.7-4.1)	(0.5-2.7)	—
Number of cases	1	1	13	8	10	
> 24.4						
Relative risk[a]	0.5	1.1	1.4	1.2	2.3	1.4[a,b]
95% confidence interval	(0.1-2.2)	(0.3-3.3)	(0.7-3.0)	(0.4-3.6)	(1.0-5.6)	(0.8-2.3)
Number of cases	2	4	16	4	9	
Percent change in BMI from age 50 to baseline						
Relative risk[a,c]	0.3	0.7	1	1.3	1.4[d]	
95% confidence interval	(0.1-1.2)	(0.3-1.7)	—	(0.6-2.6)	(0.8-2.6)	

[a] Adjusted for age, smoking status, and physical activity.
[b] Adjusted for percent change in BMI from age 50 to baseline.
[c] Adjusted for BMI at age 50.
[d] P trend = 0.01.

were not materially different from those presented for regional or disseminated disease (data not shown). This suggests that these factors are associated more strongly with the most clinically relevant disease.

Subclinical prostate cancer might influence weight, smoking habit, or physical activity, and thus reverse the temporal implications of the cohort study design. To assess this potential bias, we excluded cases diagnosed during the first two years of follow-up and then refit the main model in Table 6. Point estimates were essentially unchanged (data not shown), which suggests subclinical disease was unlikely to influence strongly our results.

Cigar smoking and change in BMI from age 50 to baseline also were evaluated in multivariate models. After adjustment for age, BMI, cigarette smoking, and physical activity, the RR for cigar smoking was attenuated (RR = 1.4, CI = 0.8-2.4). When percent change in BMI from age 50 to baseline was included in a model with age, BMI (at baseline), cigarette smoking, and physical activity, the RRs were attenuated (*e.g.*, RR = 1.2 for a gain of greater than

10 percent compared with a change of less than five percent; CI = 0.6-2.1) and the trend test was no longer statistically significant ($P = 0.1$). However, in a similar model which included BMI at age 50 (instead of BMI at baseline), the associations for both BMI at age 50 (RR = 1.9 for the upper quartile; P trend = 0.09) and percent change in BMI from age 50 to baseline (*e.g.*, RR = 1.4 for a gain of more than 10 percent compared with a change of less than five percent; P trend = 0.01; see bottom row of Table 6) became stronger. Further evaluation of the interaction between BMI at age 50 (split at the median value) and percent change in BMI from age 50 to baseline (Table 6) suggests that a decrease in BMI may be associated with a decreased risk of prostate cancer even after stratifying by BMI at age 50, although low study power precludes any strong conclusions. In contrast, men with a BMI at age 50 of greater than 24.4 kg/m^2 and who had a greater than 10 percent gain in BMI were at the highest risk of prostate cancer (RR = 2.3, CI = 1.0-5.6). In a parallel set of analyses, there was no interaction between BMI at age 25 and percent change in BMI from age 25 to baseline and prostate cancer risk (data not shown).

Discussion

Smoking and alcohol use

We found a dose-response association between number of cigarettes currently smoked and prostate cancer risk. The risk was greatest for current smokers, as former smokers had only a slightly elevated risk. Cigar smoking, but not pipe smoking, also was associated positively with risk, although the risk estimate was attenuated after controlling for cigarette smoking. Of at least 15 case-control studies[17-31] which have assessed this association, only two have reported a positive association[20,26] However, eight of these studies were hospital-based[17,18,21,24,25,27,30,31] and the two positive associations[20,26] were found in population-based studies, suggesting the possibility of bias from over-representation of smokers in hospital-based control groups. Results from prospective cohort studies have been only slightly more supportive of an association: three of seven mortality studies[32-38] and two of six incidence studies[39-44] have shown a positive association with smoking.

It is not clear why the estimates found here are somewhat higher than previously reported. No prior studies of smoking and prostate cancer have specifically focused on older men (the median age at diagnosis here was 78.8 years with a range of 66 to 93). There is some limited evidence that there may be differential effects for hormonally related risk factors for prostate cancer between younger (< 70 years) and older men (70+ years).[45,46] In addition, this is the first study to report that the association with smoking was much stronger with more advanced or aggressive disease. To our knowledge, only the hospital-based case-control study by Talamini *et al*[31] reported their results specifically for older (70+ years) men with advanced disease, and they found no association. Prior studies may have failed to detect an association because of a high percentage of localized or non-aggressive cases. This interpretation is in part supported by results from cohort studies of fatal prostate cancer, which have been somewhat more consistent in finding a positive association with smoking.

Cigarette smoking in men has been associated inconsistently with elevated levels of endogenous testosterone or estrogen,[47,48] and more consistently to elevated levels of the adrenal androgen androstenedione.[47-49] In a nested case-control study with 14 years of follow-up,[50] baseline (pre-diagnostic) levels of androstenedione were greater in men who later developed prostate cancer compared with controls after adjusting for age, smoking, and BMI, and thus androstenedione might be a possible mechanism linking smoking and prostate cancer. However, the androstenendione association has been evaluated only prospectively in the one study and therefore needs to be confirmed. Alternatively, tobacco constituents could have a direct role in prostate carcinogenesis; for example, N-nitroso compounds have been reported to induce prostate cancers in animal models.[51] Smokers compared with non-smokers, however, have been reported to have lower vegetable consumption and higher intakes of total fat and meat, and these risk factors might confound any smoking association.[3] We did not have any data on diet to assess this possibility.

We could find no association between alcohol consumption in general or with specific types of alcohol (beer, wine, liquor) and prostate cancer risk. Most previous studies[16,19,23,36,44] also have reported either a weak or no association with prostate cancer risk.

Body mass

We found a suggestive positive association with BMI and risk of prostate cancer, which was stronger for advanced or aggressive disease compared with localized disease at diagnosis. We also found that the greater the increase in BMI between age 50 and baseline the greater the risk of prostate cancer; this risk was somewhat attenuated when included in a multivariate model which also included baseline BMI. However, when we modeled the interaction between BMI at age 50 and percent change in BMI from age 50 to baseline, there was a positive association with percent change in BMI which was stronger in men who were heavier at age 50. There was no association with percent change in BMI from age 25 to baseline. Only three case-control studies have reported a positive association with overweight,[25,29,52] while most have reported a null association,[16,18,23,45,53-58] and there has been

little difference between results of hospital-based *cf* population-based studies. In contrast, cohort studies have been more suggestive: positive associations were observed in all mortality studies[59-61] and two of five incidence studies.[39,40,42,43,62] BMI reflects both fat and lean tissue, and Severson and colleagues[62] reported in a prospective cohort study that area of muscle in the arm better predicted prostate cancer incidence than the area of fat in the arm, and higher muscle mass may reflect higher endogenous levels of androgens.[63] We did not have data on other anthropometric measurements beyond height and weight.

To our knowledge, no prior studies have evaluated the role of weight gain (here measured as percent change in BMI) over the lifespan and risk of prostate cancer. Our results, if confirmed, suggest that more recent weight gain (since age 50), particularly in heavier men, may be of greater etiologic importance. In addition, the possibility of a protective effect of weight loss after age 50 is intriguing since it suggests a potential intervention for the primary prevention of prostate cancer. The exact biologic underpinnings to these findings, if real, are not known, but a hormonal mechanism seems plausible, although other mechanisms (*e.g.*, insulin or other growth factors) need to be considered.

Physical activity

We found a positive association between increasing level of physical activity and prostate cancer risk. This association was independent of smoking and BMI and also was associated more strongly with non-localized or aggressive disease at diagnosis. Three hospital-based case-control studies have reported an inverse (protective) association[25,64,65] while of three population-based case-control studies, two showed a positive association[16,57] and one showed a null association.[58] Cohort studies have also been inconsistent: three studies found a positive association[39,66,67] and four studies found an inverse association.[41,68-70] Part of the inconsistency may be due to when physical activity was assessed. Of the four studies which assessed physical activity during early adulthood (mainly college athletics), three[39,66,67] reported a positive association and one a null association.[58] Of studies which have assessed occupational physical activity during adulthood, one showed a positive association,[57] three showed an inverse association[64,65,68] and three showed a null association.[41,58,69] However, after adjustment for confounding, one of the studies showing an inverse association became null;[65] the other two studies reporting an inverse association did not adjust for any factors beyond age. Finally, of the studies assessing leisure time or recreational activity during adulthood, four have reported an inverse association[25,41,69,70] and one a null association.[58] However, few studies have focused specifically on physical activity during retirement (here both leisure time and home maintenance activity) or in the context of physical function.

It is not clear why we found a positive association. Our physical activity measure was relatively crude and we did not have data on its validity or reliability. While we did not have data on activity level on the job, the vast majority of men had already retired (77 percent), and only seven percent were employed full-time. Not taking into account physical activity from a job will have misclassified some men. However, there were no differences in level of physical activity by employment status, and exclusion of working men did not alter the positive association with physical activity. In addition, higher levels of physical activity using this measure are related inversely to all-cause mortality over three and six years of follow-up in this cohort[11] and the measure also is associated inversely with breast cancer incidence in women from this cohort.[71] It could be that inactive, chronically ill older men might either be under less surveillance for prostate cancer because of other clinical priorities or may be on diets which might reduce the risk of prostate cancer (*e.g.*, restricted intake of meat and fat).

Acute, strenuous exercise appears to increase androstenedione levels[72,73] but has not shown a consistent effect on testosterone levels.[72-75] Basal hormonal levels may be of more relevance, and trained athletes (*e.g.*, distance runners) have been found to have lower basal levels of circulating testosterone[76-78] and higher levels of androstenedione[78] compared with sedentary controls. The former suggests that physical activity should be protective for prostate cancer while the latter suggests the possibility of an increase in risk. However, no effects on testosterone, sex hormone binding globulin, or dehydroepiandrosterone were found after 14 weeks of training in middle-aged men who were originally sedentary even though there was a significant improvement in insulin sensitivity, plasma HDL, triglycerides, and adiposity.[79] We are not aware of comparable data for androstenedione. The relevance of these data to elderly persons with only very moderate levels of physical activity is not known.

Conclusions

In summary, we found a positive association between cigarette smoking and prostate cancer risk, which was independent of BMI and physical activity and was associated more strongly with aggressive or advanced disease. BMI was suggested to be associated positively with risk, also more strongly for aggressive disease. Percent change in BMI from age 50 was associated positively with risk, and the association was most pronounced in heavier men. These findings support a hormonal etiology for prostate cancer. Physical activity (from leisure and home maintenance activities) was associated positively with risk, which confirms some prior reports, although most studies, excluding studies of activity level in early adulthood, have

found a protective or null association. Nevertheless, this finding remains without a credible biologic mechanism. Further studies on these factors, particularly in the context of diet, should better clarify the these associations.

Acknowledgements — We thank Deborah Rice, Brian C.-H. Chiu, and Jo Young from the Department of Preventive Medicine and Environmental Health and Kathleen McKeen and Diana Wagner from the State Health Registry of Iowa for their helpful contributions.

References

1. Kosary CL, Ries LAG, Miller BA, Hankey BF, Harras A, Edwards BK, eds. *SEER Cancer Statistics Review, 1973-1992: Tables and Graphs, National Cancer Institute.* Bethesda, MD (USA): National Insitutes of Health, 1995 NIH Pub. No. 96-2789.
2. Muir C, Waterhouse J, Mack T, *et al.* eds. *Cancer Incidence in Five Continents.* Vol. 5. Lyon, France: International Agency for Research on Cancer, 1987; IARC Sci. Pub. No. 88.
3. Nomura AMY, Kolonel L. Prostate cancer: a current perspective. *Epidemiol Rev* 1991; 13: 200-27.
4. Pienta KJ, Esper PS. Risk factors for prostate cancer. *Ann Int Med* 1993; 118: 793-803.
5. Ross RK, Paganini-Hill A, Henderson BE. The etiology of prostate cancer: what does the epidemiology suggest? *Prostate* 1983; 4: 333-44.
6. Wilding G. The importance of steroid hormones in prostate cancer. *Cancer Surv* 1992; 14: 113-30.
7. Geller J. Basis for hormonal management of advanced prostate cancer. *Cancer* 1993; 71: 1039-45.
8. Henderson BE, Ross RK, Pike MC, Casagrande JT. Endogenous hormones as a major risk factor in human cancer. *Cancer Res* 1982; 42: 3232-9.
9. Cornoni-Huntley J, Brock DB, Ostfeld AM, Taylor JO, Wallace RB. *Established Populations for the Epidemiologic Study of the Elderly. Resource Data Book.* Bethesda, MD (USA): National Institutes of Health, 1986; NIH Pub. No. 86-2443.
10. Cornoni-Huntley J, Ostfeld AM, Taylor JO, *et al.* Established populations for epidemiologic studies of the elderly: study design and methodology. *Aging* 1993; 5: 27-37.
11. Simonsick EM, Lafferty ME, Phillips CL, *et al.* Risk due to inactivity in physically capable older adults. *Am J Public Health* 1993; 83: 1443-50.
12. Rosow I, Breslau N. A Guttman health scale for the aged. *J Gerontol* 1966; 21: 556-9.
13. Percy C, Van Holten V, Muir C, eds. *International Classification of Diseases for Oncology, Second Edition.* Geneva, Switzerland: World Health Organization, 1990.
14. Breslow N, Day N. *Statistical Methods in Cancer Research. Volume II. The Design and Analysis of Cohort Studies.* Lyon, France: International Agency for Cancer Research, 1987; IARC Sci. Pub. No. 82.
15. Frome EL. The analysis of rates using Poisson regression models. *Biometrics* 1983; 39: 665-74.
16. West DW, Slattery ML, Robison LM, French TK, Mahoney AW. Adult dietary intake and prostate cancer risk in Utah: a case-control study with special emphasis on aggressive tumors. *Cancer Causes Control* 1991; 2: 85-94.
17. Schwartz D, Flamant R, Lellouch J, Denoix PF. Results of a French survey on the role of tobacco, particularly inhalation, in different cancer sites. *JNCI* 1961; 26: 1085-108.
18. Wynder EL, Mabuchi K, Whitmore WF Jr. Epidemiology of cancer of the prostate. *Cancer* 1971; 28: 344-60.
19. Williams RR, Horm JW. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: Interview study from the Third National Cancer Survey. *JNCI* 1977; 58: 525-47.
20. Schuman LM, Mandel J, Blackard C, Bauer H, Scarlett J, McHugh R. Epidemiologic study of prostatic cancer: Preliminary report. *Cancer Treatment Rep* 1977; 61: 181-6.
21. Niijima T, Koiso K. Incidence of prostatic cancer in Japan and Asia. *Scand J Urol Nephrol* 1980; 55(Suppl): 17-21.
22. Mishina T, Watanabe H, Araki H, Nakao M. Epidemiological study of prostatic cancer by matched-pair analysis. *Prostate* 1985; 6: 423-36.
23. Ross RK, Shimizu H, Paganini-Hill A, Honda G, Henderson BE. Case-control studies of prostate cancer in blacks and whites in Southern California. *JNCI* 1987; 78: 869-74.
24. Checkoway H, DiFerdinando G, Hulka BS, Mickey DD. Medical, life-style, and occupational risk factors for prostate cancer. *Prostate* 1987; 10: 79-88.
25. Yu H, Harris RE, Wynder EL. Case-control study of prostate cancer and socioeconomic factors. *Prostate* 1988; 13: 317-25.
26. Honda GD, Bernstein L, Ross RK, Greenland S, Gerkins V, Henderson BE. Vasectomy, cigarette smoking, and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. *Br J Cancer* 1988; 57: 326-31.
27. Newell GR, Fueger JJ, Spitz MR, Babaian RJ. A case-control study of prostate cancer. *Am J Epidemiol* 1989; 130: 395-8.
28. Slattery ML, Schumacher MC, West DW, Robison LM, French TK. Food-consumption trends between adolescent and adult years and subsequent risk of prostate cancer. *Am J Clin Nutr* 1990; 52: 752-7.
29. Fincham SM, Hill GB, Hanson J, Wijayasinghe C. Epidemiology of prostatic cancer: A case-control study. *Prostate* 1990; 17: 189-206.
30. La Vecchia C, Negri E, D'Avanzo B, Franceschi S, Boyle P. Dairy products and the risk of prostatic cancer. *Oncology* 1991; 48: 406-10.
31. Talamini R, Franceschi S, La Vecchia C, Guarneri S, Negri E. Smoking habits and prostate cancer: a case-control study in northern Italy. *Prev Med* 1993; 22: 400-8.
32. Hammond EC. Smoking in relation to the death rates of one million men and women. *NCI Monogr* 1966; 19: 127-204.
33. Doll R, Peto R. Mortality in relation to smoking: 20 years' observation on male British doctors. *Br Med J* 1976; 2: 1525-36.
34. Hirayama T. Epidemiology of prostate cancer with special reference to the role of diet. *NCI Monogr* 1979; 53: 149-55.
35. Carstensen JM, Pershagen G, Eklund G. Mortality in relation to cigarette and pipe smoking: 16 years' observation of 25000 Swedish men. *J Epidemiol Community Health* 1987; 41: 166-72.
36. Hsing AW, McLaughlin JK, Schuman LM, *et al.* Diet, tobacco use, and fatal prostate cancer: Results from the Lutheran Brotherhood Cohort Study. *Cancer Res* 1990; 50: 6836-40.
37. Hsing AW, McLaughlin JK, Hrubec Z, Blot WJ, Fraumeni JF Jr. Tobacco use and prostate cancer: 26-year follow-up of US veterans. *Am J Epidemiol* 1991; 133: 437-41.
38. Coughlin SS, Neaton JD, Sengupta A. Cigarette smoking as a predictor of death from prostate cancer in 348,874 men

2063634046

screened for Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 1996; **143**: 1002-6.

39. Whittemore AS, Paffenbarger RS Jr, Anderson K, Lee JE. Early precursors of site-specific cancers in college men and women. *JNCI* 1985; **74**: 43-51.
40. Thompson MM, Garland C, Barrett-Connor E, Khaw KT, Friedlander NJ, Wingard DL. Heart disease risk factors, diabetes, and prostatic cancer in an adult community. *Am J Epidemiol* 1989; **129**: 511-7.
41. Severson RK, Nomura AM, Grove JS, Stemmermann GN. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. *Cancer Res* 1989; **49**: 1857-60.
42. Mills PK, Beeson WL, Phillips RL, Fraser GE. Cohort study of diet, lifestyle, and prostate cancer in Adventist men. *Cancer* 1989; **64**: 598-604.
43. Le Marchand L, Kolonel LN, Wilkens LR, Myers BC, Hirohata T. Animal fat consumption and prostate cancer: A prospective study in Hawaii. *Epidemiology* 1994; **5**: 276-82.
44. Hiatt RA, Armstrong MA, Klatsky AL, Sidney S. Alcohol consumption, smoking and other risk factors and prostate cancer in a large health plan cohort in California (United States). *Cancer Causes Control* 1994; **5**: 66-72.
45. Kolonel LN, Yoshizawa CN, Hankin JH. Diet and prostatic cancer: A case-control study in Hawaii. *Am J Epidemiol* 1988; **127**: 999-1012.
46. Zumoff B, Levin J, Strain GW, *et al.* Abnormal levels of plasma hormones in men with prostate cancer: evidence toward a 'two-disease theory.' *Prostate* 1982; **3**: 579-88.
47. Dai WS, Gutai JP, Kuller LH, Cauley JA for the MRFIT Research Group. Cigarette smoking and serum sex hormones in men. *Am J Epidemiol* 1988; **128**: 796-805.
48. Barrett-Conner E, Khaw KT. Cigarette smoking and increased endogenous estrogen levels in men. *Am J Epidemiol* 1987; **126**: 187-92.
49. Hautanen A, Adlercreutz H. Hyperinsulinemia, dyslipidaemia, and exaggerated adrenal androgen response to adrenocorticotropin in male smokers. *Diabetologia* 1993; **36**: 1275-81.
50. Barrett-Conner E, Garland C, McPhillips JB, Khaw KT, Wingard DL. A prospective, population-based study of androstenedione, estrogens, and prostatic cancer. *Cancer Res* 1990; **50**: 169-73.
51. Pour P. Prostatic cancer induced in MRC rats by N-nitrosobis(2-oxopropyl)amine and N-nitroso-bis(2-hydroxypropyl)amine. *Carcinogenesis* 1983; **4**: 49-55.
52. Talamini R, La Vecchia C, Decarli A, Negri E, Franceschi S. Nutrition, social factors and prostate cancer in a northern Italian population. *Br J Cancer* 1986; **53**: 817-21.
53. Greenwald P, Damon A, Kirmss V, Polan AK. Physical and demographic features of men before developing cancer of the prostate. *JNCI* 1974; **53**: 341-6.
54. Graham S, Haughey B, Marshall J, *et al.* Diet in the epidemiology of carcinoma of the prostate gland. *JNCI* 1983; **70**: 687-92.
55. Mettlin C, Selenskas S, Natarajan N, Huben R. Beta-carotene and animal fats and their relationship to prostate cancer risk. *Cancer* 1989; **64**: 605-12.
56. La Vecchia C, Negri E, Parazzini F, *et al.* Height and cancer risk in a network of case-control studies from Northern Italy. *Int J Cancer* 1990; **45**: 275-9.
57. Le Marchand L, Kolonel LN, Yoshizawa CN. Lifetime occupational physical activity and prostate cancer risk. *Am J Epidemiol* 1991; **133**: 103-11.
58. Whittemore AS, Kolonel LN, Wu AH, *et al.* Prostate cancer in relation to diet, physical activity, and body size in Blacks, Whites, and Asians in the United States and Canada. *JNCI* 1995; **87**: 652-61.
59. Lew EA, Garfinkel L. Variations in mortality by weight among 750,000 men and women. *J Chron Dis* 1979; **32**: 563-76.
60. Snowdon DA, Phillips RL, Choi W. Diet, obesity, and risk of fatal prostate cancer. *Am J Epidemiol* 1984; **120**: 244-50.
61. Garfinkel L. Overweight and mortality. *Cancer* 1986; **58**: 1826-9.
62. Severson RK, Grove JS, Nomura AM, Stemmermann GN. Body mass and prostatic cancer: a prospective study. *BMJ* 1988; **297**: 713-5.
63. Henderson BE. Summary report of the Sixth Symposium on Cancer Registries and Epidemiology in the Pacific Basin. *JNCI* 1990; **82**: 1186-90.
64. Brownson RC, Chang JC, Davis JR, Smith CA. Physical activity on the job and cancer in Missouri. *Am J Public Health* 1991; **81**: 639-42.
65. Dosemeci M, Hayes RB, Vetter R, *et al.* Occupational physical activity, socioeconomic status, and risks of 15 cancer sites in Turkey. *Cancer Causes Control* 1993; **4**: 313-21.
66. Polednak AP. College athletics, body size, and cancer mortality. *Cancer* 1976; **38**: 382-7.
67. Paffenbarger RS Jr, Hyde RT, Wing AL. Physical activity and incidence of cancer in diverse populations: a preliminary report. *Am J Clin Nutr* 1987; **45**: 312-7.
68. Vena JE, Graham S, Zielezny M, Brasure J, Swanson MK. Occupational exercise and risk of cancer. *Am J Clin Nutr* 1987; **45**: 318-27.
69. Albanes D, Blair A, Taylor PR. Physical activity and risk of cancer in the NHANES I population. *Am J Public Health* 1989; **79**: 744-50.
70. Lee IM, Paffenbarger RS Jr, Hsieh C-c. Physical activity and risk of prostatic cancer among college alumni. *Am J Epidemiol* 1992; **135**: 169-79.
71. Cerhan J, Chiu B, Wallace R, *et al.* Systolic blood pressure, physical activity and risk of breast cancer in elderly women [Abstract]. *Am J Epidemiol* 1996; **143**: S71.
72. Dessypris A, Kuoppasalmi K, Adlercreutz H. Plasma cortisol, testosterone, androstenedione and luteinizing hormone (LH) in a non-competitive marathon run. *J Steroid Biochem* 1976; **7**: 33-7.
73. Velardo A, Pantaleoni M, Valerio L, Barini A, Marrama P. *Exp Clin Endocrinol* 1991; **97**: 99-101.
74. Aakvaag A, Sand T, Ostad PK, *et al.* Hormonal changes in serum in young men during prolonged physical strain. *Eur J Appl Physiol* 1978; **39**: 283-91.
75. Sutton JR, Coleman MH, Casey J, *et al.* Androgen responses during physical exercise. *Br Med J* 1973; **1**: 520-2.
76. Morville R, Pesquies PC, Guezennec CY, Serrurier BD, Guignard M. Plasma variations in testicular and andrenal androgens during prolonged physical exercise in man. *Ann Endocrinol (Paris)* 1979; **40**: 501-10.
77. Wheeler GD, Wall SR, Belcastro AN, Cumming DC. Reduced serum testosterone and prolactin levels in male distance runners. *JAMA* 1984; **252**: 514-6.
78. Hackney AC, Sinning WE, Bruot BC. Reproductive hormonal profiles of endurance-trained and untrained males. *Med Sci Sports Exerc* 1988; **20**: 60-5.
79. Houmard JA, McCulley C, Shinebarger MH, Bruno NJ. Effects of exercise training on plasma androgens in men. *Horm Metab Res* 1994; **26**: 291-300.